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(73) Proprietors:

- **CEPHALON, INC.**
West Chester, PA 19380-4245 (US)
- **KYOWA HAKKO KOGYO CO., LTD.**
Chiyoda-ku, Tokyo 100 (JP)

(72) Inventors:

- **LEWIS, Michael, E.**
West Chester Pennsylvania 19382 (US)
- **NEFF, Nicola**
Rose Valley, PA 19086 (US)
- **ROBERTS-LEWIS, Jill**
West Chester Pennsylvania 19382 (US)
- **MURAKATA, Chikara 2-11-2-702, Bessho**
Tokyo 192-03 (JP)
- **SAITO, Hiromitsu**
Kawasaki-shi Kangawa (JP)
- **MATSUDA, Yuzuru 1-22-7, Nukuiminami-cho**
Tokyo 184 (JP)

- **KAUER, James, C.**
Kennett Square, PA 19348 (US)

(74) Representative: **Perry, Robert Edward et al**
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH (GB)

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- The J. of Antibiotics, Vol. 32, No. 8, issued August 1986, NAKANISHI et al., "K-252b, c and d, Potent Inhibitors of Protein Kinase c from Microbial Origin", pgs. 1066-1071, see Fig. 3, pg. 1069.
- **CHEMICAL ABSTRACTS**, Vol. 107, issued 1987, Abstract No. 236750y; & JP,A,62 155 284 (HIRATA) 10 July 1987.
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- ANNALS OF THE N.Y. ACAD. OF SCIENCES, Vol. 559, issued 05 July 1989, ABE et al., "Arachidonic Acid Metabolism in Ischemic Neuronal Damage", pgs. 259-268, see pgs. 260, 264 and 267.
- Neuroscience Letters, Vol. 108, issued 01 January 1990, G.D. BORASIO, "Differential Effect of the Protein Kinase Inhibitor K-252a on the in Vitro Survival of Chick Embryonic Neurons", pgs. 207-212, see Abstract pg. 207.
- The J. of Pharmacology and Exp. Therapeutics, Vol. 257, No. 2, issued 02 January 1991, NABESHIMA et al., "Staurosporine Facilitates Recovery from the Basal Forebrain-Lesion-Induced Impairment of Learning and Deficit of Cholinergic Neurons in Rats", pgs. 562-566, see pg. 566, first ten lines.

DescriptionBackground of the Invention

Protein kinases are a broad class of enzymes which act to modify chemically many cellular proteins, by phosphorylation of amino acids.

Inhibitors of protein kinases are structurally varied, and have variable (and sometimes contradictory) effects on the nervous system and other tissues. A given protein kinase inhibitor may influence more than one protein kinase. For example, K-252a, an alkaloid-like material isolated from the culture broth of *Nocardopsis sp.* and *Actinomadura sp.* was originally reported to be a protein kinase C inhibitor, but was subsequently found also to inhibit protein kinases A and G, myosin light-chain kinase, and trk (a tyrosine kinase activated by nerve growth factor [NGF], the latter a neurotrophic protein which promotes the survival of peripheral, sensory and sympathetic neurons). Consistent with this latter effect, K-252a blocks the neurotrophic actions of NGF on PC-12 cells (chromaffin cells from rat adrenal medullary tumors, pheochromocytomas), and promotes the survival of dorsal root ganglion neurons and hippocampal neurons. However, it has been found to be cytotoxic at a wide range of concentrations, leading some investigators to conclude that it has limited usefulness *in vivo*.

A microbial alkaloid related to K-252a, staurosporine, also has a variety of effects on different protein kinases and cell types. Staurosporine was found to have NGF-like effects on PC-12 cells, and to protect the gerbil hippocampus from post-ischemic injury. It is able to reverse damage to cholinergic neurons in the rat basal forebrain.

K-252a and staurosporine have been proposed as tumor inhibitors. Staurosporine has been offered as an insecticide. Derivatives of staurosporine, with a hydrocarbonyl or acyl substituent at the methylamine nitrogen, have been made and proposed for tumour inhibition, inflammation inhibition, immunomodulation, and treatment of diseases of the cardiovascular and central nervous systems.

Nabeshima *et al.*, The Journal and Exp. Therapeutics 257:562-6 (1991), disclose that the use of staurosporine partially reverse reduced choline acetyltransferase activity.

Summary of the Invention

According to one aspect of the present invention, a functional derivative of K-252a is used for the manufacture of a medicament for use in enhancing, in a mammal, the function of a cholinergic neuron. The functional derivatives used in this invention are the respective compounds, of formulae II, III and IV, defined in claim 1.

According to a second aspect of the present invention, novel compounds are those of formulae II-4, II-14, II-38, II-45, II-49 and II-51 as defined in claim 1, and also compounds of formula V as defined in claim 12.

Description of the invention

In the definitions of the groups in formula (V), C₁₋₆ alkyl means a straight-chain or branched alkyl group having 1 to 6 carbon atoms, preferably 1 to 3 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl or hexyl. C₆₋₁₀ aryl means an aryl group having 6 to 10 carbon atoms, such as phenyl or naphthyl.

Formula V compounds can be in the form of pharmaceutically-acceptable salts. The pharmaceutically-acceptable salts of compounds (V) include pharmaceutically-acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts and amino-acid addition salts.

Examples of the pharmaceutically-acceptable acid addition salts are inorganic acid addition salts such as hydrochloride, sulfate and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, tartrate and citrate. Examples of the pharmaceutically-acceptable metal salts are alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminium salt, and zinc salt. Examples of the pharmaceutically-acceptable ammonium salts are ammonium salt and tetraethylammonium salt. Examples of the pharmaceutically-acceptable organic amine addition salts are salts with morpholine and piperidine. Examples of the pharmaceutically-acceptable amino-acid addition salts are salts with lysine, glycine and phenylalanine.

The invention provides a means for enhancing the function of cholinergic neurons, by administering to a mammal, e.g. a human, a therapeutic amount of one of the K-252a derivatives. The therapy may be given in conjunction with a neurotrophic factor, preferably a member of the neurotrophic family, and most preferably nerve growth factor (NGF). The neurotrophic family is a group of proteins with significant homology to NGF and includes, in addition to NGF, brain-derived neurotrophic factor (BDNF; Leibrock *et al.*, Nature 341:149-152, 1989); neurophil-3 (NT-3; Hohn *et al.*, Nature 344:339-341, 1990); and neurotrophic-5 (NT-5; Berkemeier *et al.*, Neuron 7:857-866, 1991).

By "enhancing the function of cholinergic neurons" is meant promoting cholinergic nerve cell survival, and/or nerve fibre (e.g. axonal) growth, and/or enhancing cholinergic activity of nerve cells. The therapy may involve the treatment

where cholinergic neurons are injured, compromised, undergoing axonal degeneration, or at risk of dying.

The compounds of this invention are useful for administration to humans or other mammals who suffer from neurological diseases or disturbances characterised by increased risk of neuronal cell death or dysfunction. These neurological diseases and disturbances include but are not limited to: Alzheimer's disease; motor neuron disease including amyotrophic lateral sclerosis; Parkinson's disease; stroke or other ischemic injuries; Huntingdon's disease; AIDS dementia; epilepsy; concussive or penetrating injuries of the brain or spinal cord; and peripheral neuropathies.

The functional derivative of K-252a used in this invention may possess improved solubility, absorption, transport (e.g. through the blood-brain barrier and cellular membranes), biological half-life, etc. Alternatively, or in addition, some modifications may decrease the toxicity of the molecule, or eliminate or attenuate any undesirable side-effect of the molecule.

The compounds used in this invention can be formulated into pharmaceutical compositions by admixture with pharmaceutically-acceptable non-toxic excipients and carriers. Such compositions may be prepared for use in parenteral administration, particularly in the form of liquid solutions or suspensions; for oral administration, particularly in the form of tablets or capsules; or for use intranasally, particularly in the form of powders, nasal drops or aerosols.

The composition may conveniently be administered in unit dosage form and may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in Remington's Pharmaceutical Sciences (Mack Pub. Co., Easton, PA, 1980). Formulations for parenteral administration may contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer or polyoxyethylene-polyoxypropylene copolymers may be useful excipients to control the release of the active compounds. Other potentially useful parenteral delivery systems for these active compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration contain as excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration may also include glycocholate for buccal administration, methoxyxalicylate for rectal administration, or citric acid for vaginal administration.

The materials of this invention can be employed as the sole active agent in a pharmaceutical or can be used in combination with other active ingredients, e.g., other growth factors which could facilitate neuronal survival or axonal growth in neurological diseases or disorders, for example, peripheral neuropathy.

The concentrations of the compounds described herein in a therapeutic composition will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (e.g., hydrophobicity) of the compounds employed, and the route of administration. In general terms, the compounds of this invention may be provided in an aqueous physiological buffer solution containing about 0.1 to 10% w/v compound for parenteral administration. Typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.01 mg/kg to 100 mg/kg of body weight per day. The preferred dosage of drug to be administered is likely to depend on such variables as the type and extent of progression of the neurological disease, the overall health status of the particular patient, the relative biological efficacy of the compound selected, the formulation of the compound excipients, and its route of administration.

The functional derivatives of K-252a used in the invention may be prepared *de novo* by chemical synthesis using methods known to those skilled in the art. For example, procedures used for preparation of compounds of formula II are described in US-A-4923986. Procedures used for preparation of compounds of formula III are described by Moody *et al*, J. Org. Chem. 57:2105-2114 (1992); Steglich *et al*, Angew. Chem. Int. Ed. Engl. 19:459-460 (1980); Nakanishi *et al*, J. Antibiotics 39:1066-1071 (1986); and Japanese Patent Application No. 60-295172 (1985). Further methods are described for compounds II-1, 9, 12 and 15 in Japanese Patent Application No. 60-295173 (1985); for compounds II-2, 3, 4, 24, 25 and 26 in Japanese Patent Application No. 62-327858 (1987); for compound II-20 in Japanese Patent Application No. 62-327859 (1987); and for compound II-10 in Japanese Patent Application No. 60-257652 (1985).

The following Examples illustrate how compounds for use in this invention may be prepared.

Example 1

Compound II-4

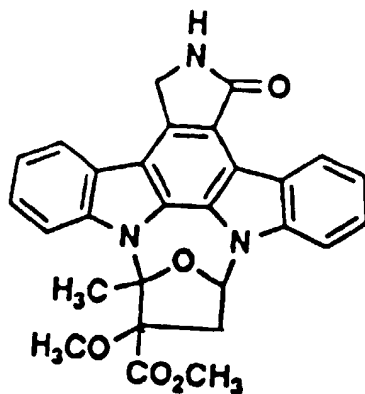
Compound A (962 mg, 2 mmol) was dissolved in a mixture of 30 ml of tetrahydrofuran and 10 ml of methanol, and then 760 mg of sodium borohydride (20 mmol) was added thereto under ice cooling, followed by stirring at the same temperature for 4 hours and further at room temperature for 12 hours. After 3N hydrochloric acid was added thereto, the solution was washed with an aqueous solution of sodium chloride and dried over magnesium sulfate, followed by evaporation of the solvent. The residue was purified by silica gel column chromatography (chloroform/methanol = 98/2) to give 882 mg (yield 97%) of compound II-4.

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Melting Point: 130-140°C

¹H-NMR (DMSO-d₆) δ (ppm): 2.032(1H, dd, J=5.0), 2.231 (3H, s), 2.967(3H, s), 3.609(1H, dd, J=7.6, 13.4Hz), 3.959(2H, m), 5.000(2H, s), 5.268(1H, t, J=5.3Hz), 7.065(1H, dd, J=4.9, 7.3Hz), 7.254-8.038 (7H, m), 8.565(1H, s), 9.206(1H, d, J=7.8Hz)

Compound A



Example 2

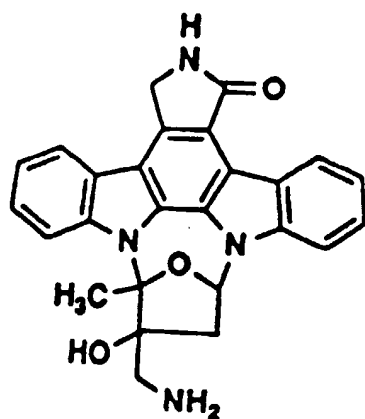
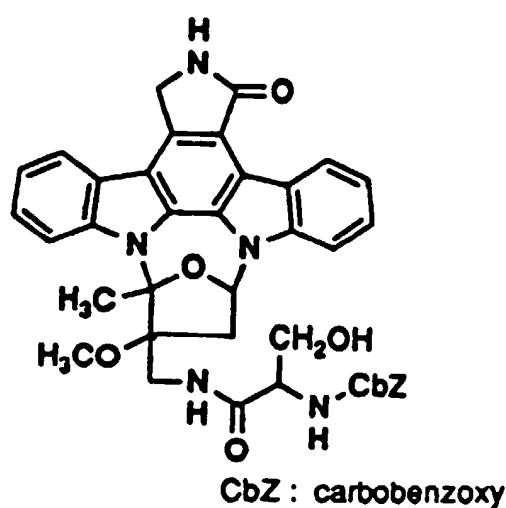
Compound II-14

Compound B (393 mg, 0.9 mmol) was dissolved in 25 ml of tetrahydrofuran, and then 3 ml of tetrahydrofuran containing 309 mg of carbobenzoxy-L-serine (1.35 mmol), 156 mg of N-oxysuccinimide (1.35 mmol), 0.1 ml of 4-methylmorpholine (0.9 mmol) and 279 mg of dicyclohexylcarbodiimide (1.35 mmol) was added under ice cooling, followed by stirring for 12 hours. The reaction mixture was filtered and the solvent was evaporated. The residue was purified by silica gel column chromatography (chloroform/methanol = 99/1) to give 429 mg (yield 72%) of Compound C.

Melting Point: 188-193°C
SIMS (m/z): 660 (M+1)⁺

Compound C (399 mg) was dissolved in 10 ml of dimethylformamide, and then 300 mg of 10% palladium on carbon was added, followed by stirring at 50°C for 7 hours in a hydrogen stream. The reaction mixture was filtered through Celite and the solvent was evaporated. The residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonium hydroxide = 90/10/1) and the obtained product was dissolved in 5 ml of tetrahydrofuran, followed by addition of 5 ml of 1.7N hydrogen chloride/ethyl acetate and 10 ml of diethyl ether. The precipitate was separated from the solution by filtration to give 234 mg (yield 69%) of Compound II-14.

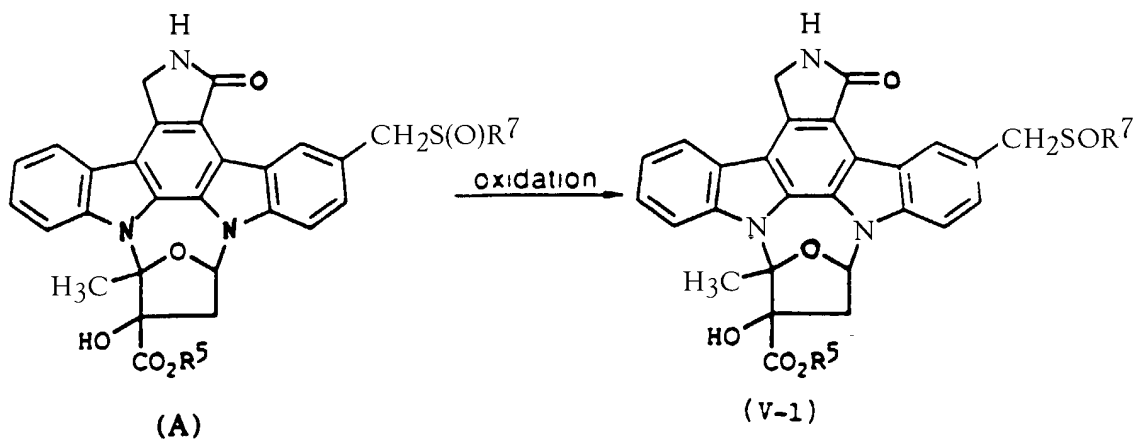
Melting Point: >300°C
¹H-NMR (DMSO-d₆ + D₂O) δ (ppm): 1.92-2.28(1H, m), 2.20 (3H, s), 2.84-3.12(7H, m), 3.40-4.20(5H, m), 5.04 (2H, s), 6.98(1H, m), 7.24-8.20(7H, m), 8.76(1H, brs), 9.22(1H, d, J=8Hz)
SIMS (m/z): 527 (M+2)⁺

Compound B**Compound C**Processes for Producing Compounds (V)

The processes for producing Compounds (V) are described below.

Process 1

Compound (V-1) [Compound (V) in which R^1 is $\text{CH}_2\text{SO}_2\text{R}^7$ and X is CO_2R^5] can be prepared by the following reaction step:



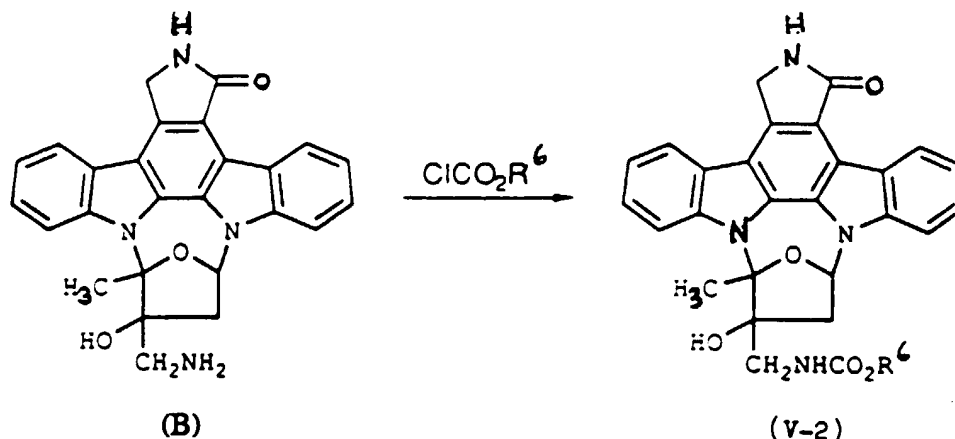
(R^5 represents $\text{C}_1\text{-C}_6$ alkyl; R^7 represents $\text{C}_1\text{-C}_6$ alkyl.)

The starting compound (A) is disclosed in Japanese Published Unexamined Patent Application No. 295588/88.

Compound (V-1) can be obtained by treatment of Compound (A) with 1 to 1.5 equivalents of an oxidant. An example of the oxidant is m-chloroperbenzoic acid. As a reaction solvent, a halogenated hydrocarbon such as methylene chloride, chloroform, or ethylene dichloride, or the like is used. The reaction is completed in 0.5 to 1 hour at -20 to 30°C .

Process 2

Compounds (V-2) [compound (V) in which R^1 is hydrogen and X is $\text{CH}_2\text{NHCO}_2\text{R}^6$] can be prepared by the following reaction step:



R^6 represents $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_6\text{-C}_{10}$ aryl.

The starting compound (B) is disclosed in Japanese Published Unexamined Patent Application No. 155285/87.

Compound (V-2) can be obtained by reaction of Compound (B) with 1 to 3 equivalents of ClCO_2R^6 in the presence of 1 to 3 equivalents of a base. An example of the base is triethylamine. As a reaction solvent, a halogenated hydrocarbon such as methylene chloride, chloroform, or ethylene dichloride, or the like is used. The reaction is completed in 0.5 to 3 hours at -10 to 30°C .

Example 3

Compound II-49

Compound (A-1; $\text{R}^5=\text{CH}_3$ and $\text{R}^7=\text{C}_2\text{H}_5$) (27 mg, 0.05 mmol) was dissolved in 1 ml of chloroform, and then 10 mg (0.06 mmol) of m-chloroperbenzoic acid was added thereto under ice cooling, followed by stirring at the same temperature for 45 minutes. After dilution with chloroform, the mixture was washed successively with a 8% aqueous solution of sodium thiosulfate, a saturated aqueous solution of sodium bicarbonate, water, and a saline solution, and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (chloroform/methanol = 95/5) to give 17.7 mg (yield 62%) of Compound II-49.

$^1\text{H-NMR}$ (DMSO-d_6) δ (ppm): 1.298(3H, t, $J=7.5\text{Hz}$), 2.037 (1H, dd, $J=5.0, 14.1\text{Hz}$), 2.153(3H, s), 3.096(2H, q, $J=7.5\text{Hz}$), 3.266 (2H, s), 3.929(3H, s), 4.985 (1H, d, $J=17.0\text{Hz}$), 5.043(1H, d, $J=17.0\text{Hz}$), 6.348(1H, s), 7.147 (1H, dd, $J=4.9, 7.1\text{Hz}$), 7.345-8.070(6H, m), 8.612 (1H, s), 9.232(1H, d, $J=1.5\text{Hz}$)

FAB-MS (m/z): 574 ($\text{M}+1$)⁺

Example 4

Compound II-38

Compound (B) (43.8 mg, 0.1 mmol) was dissolved in 1 ml of tetrahydrofuran, and then 15 μl phenyl chloroformate and 28 μl (0.2 mmol) of triethylamine were added thereto, followed by stirring for 50 minutes under ice cooling. After dilution with tetrahydrofuran, the mixture was washed with a saline solution, and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (chloroform/methanol = 99/1) to give 27.8 mg (yield 50%) of Compound II-38.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.111(3H, s), 2.890(1H, brd, $J=13.7\text{Hz}$), 3.262(1H, dd, $J=7.5, 13.9\text{Hz}$), 3.742(1H, d, $J=13.4\text{Hz}$), 3.967 (1H, d, $J=12.9\text{Hz}$), 4.582(1H, d, $J=16.3\text{Hz}$), 5.342(1H, brs), 5.906(1H, brs), 6.550 (1H, brs), 7.005-8.042(12H, m), 8.596(1H, d, $J=7.6\text{Hz}$)

FAB-MS (m/z): 559 ($\text{M}+1$)⁺

Example 5

(The synthesis of Compound H from Compound C is shown in Fig. 2.)

5 Compound II-39

Compound (C) (Japanese Published Unexamined Patent Application No. 295588/88) (20 mg, 0.035 mmol) was dissolved in 1 ml of chloroform, and then 14.6 μ l (0.105 mmol) of triethylamine and 13.9 μ l (0.175 mmol) of ethyl isocyanate were added thereto, followed by stirring at room temperature for 2 hours. To the solution was added 1 ml of methanol, followed by dilution with chloroform. The mixture was washed successively with water and a saline solution, and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (chloroform/methanol = 98/2) to give 21 mg (yield 84% of Compound (D)).

¹H-NMR (CDCl₃) δ (ppm): 1.195(3H, t, J=7.2Hz), 1.222(3H, t, J=7.2Hz), 1.664(3H, s), 2.194(3H, s), 2.555(3H, s), 3.346(4H, q, J=7.2Hz), 3.820(1H, dd, J=7.5, 14.6Hz), 3.938(3H, s), 5.036(1H, d, J=17.7Hz), 5.125(1H, d, J=17.2Hz), 6.745(1H, dd, J=4.8, 7.4Hz), 7.260-7.898(5H, m), 8.690(1H, d, J=1.9Hz)

FAB-MS (m/z): 724 (M+1)⁺

Compound (D) (9 mg, 0.012 mmol) was dissolved in a mixture of 0.2 ml of tetrahydrofuran and 0.2 ml of methanol, and then 2 μ l of 28% sodium methoxide/methanol was added thereto, followed by stirring at room temperature for 10 minutes. To the solution was added 0.1 ml of a 5% aqueous solution of citric acid, followed by dilution with chloroform. The mixture was washed successively with water and a saline solution, and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (chloroform/methanol = 9/1) to give 8 mg of Compound II-39.

¹H-NMR (DMSO-d₆) δ (ppm): 1.086(3H, t, J=7.1Hz), 1.099 (3H, t, J=7.1Hz), 1.948(1H, dd, J=4.8, 14.1Hz), 2.107(3H, s), 3.158(4H, m), 3.910(3H, s), 4.880(1H, d, J=17.7Hz), 4.931(1H, d, J=16.9Hz), 7.028(1H, dd, J=5.0, 7.1Hz), 7.332-8.287(5H, m), 8.838(1H, d, J=2.1Hz)

FAB-MS (m/z): 640 (M+1)⁺

Example 635 Compounds II-51 and II-56

Compound (E) (Japanese Published Unexamined Patent Application No. 295588/88; *supra*) (60.7 mg, 0.1 mmol) was dissolved in a mixture of 5 ml of chloroform and 1 ml of methanol, and then 11 mg (0.3 mmol) of sodium borohydride was added thereto under ice cooling, followed by stirring at the same temperature for 15 minutes. After dilution with chloroform, the mixture was washed successively with water and a saline solution, and dried over potassium carbonate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (Chloroform/methanol/triethylamine = 98/2/0.5) to give 36 mg (yield 59%) of Compound (F).

¹H-NMR (DMSO-d₆) δ (ppm): 1.650(3H, s), 2.027(1H, dd, J=4.9, 14.5Hz), 2.126(3H, s), 3.843(1H, dd, J=7.4, 14.5Hz), 3.891(3H, s), 4.607(2H, s), 4.673(2H, s), 5.125(2H, s), 7.099(1H, dd, J=5.0, 7.3Hz), 7.437-7.907(5H, m), 8.812(1H, d, J=0.8Hz)

FAB-MS (m/z): 612 (M+1)⁺

Compound (F) (159 mg, 0.26 mmol) was dissolved in 15 ml of chloroform, and then 0.8 ml (10.4 mmol) of ethanethiol and 24 mg (0.104 mmol) of camphorsulfonic acid were added thereto, followed by stirring at room temperature for 12 hours. The solution was washed successively with a saturated aqueous solution of sodium bicarbonate, water, and a saline solution, and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (ethyl acetate/toluene = 1/9 - chloroform/methanol = 99/1) to give 43 mg of Compound (G) and 75 mg of Compound (H).

55 Compound (G)

¹H-NMR (CDCl₃) δ (ppm): 1.292(3H, t, J=7.4Hz), 1.297 (3H, t, J=7.4Hz), 1.799(3H, s), 2.141(1H, dd,

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J=5.0, 14.5Hz), 2.256(3H, s), 2.532(2H, q, J=7.4Hz), 2.553(2H, q, J=7.4Hz), 2.869(3H, s), 3.971(1H, dd, J=7.5, 14.5Hz), 3.992(2H, s), 4.005 (3H, s), 4.021 (2H, s), 5.416(1H, dd, J=17.5Hz), 5.459(1H, d, J=17.4Hz), 6.989(1H, dd, J=5.1, 7.4Hz), 7.509-7.963(5H, m), 9.134(1H, d, J=1.2Hz)

5 FAB-MS (m/z): 700 (M+1)⁺

Compound (H)

10 ¹H-NMR (CDCl₃) δ (ppm): 1.294(3H, t, J=7.4Hz), 1.799(3H, s), 2.149(1H, dd, J=5.0, 14.6Hz), 2.273(3H, s), 2.533(2H, q, J=7.4Hz), 2.813 (3H, s), 3.972(1H, dd, J=7.4, 14.6Hz), 4.008 (3H, s), 4.015(2H, s), 4.951 (2H, s), 5.377(1H, d, J=17.4Hz), 5.418(1H, d, J=17.4Hz), 6.973(1H, dd, J=5.0, 7.5Hz), 7.481-8.037 (5H, m), 9.093(1H, d, J=1.2Hz)

15 FAB-MS (m/z): 656 (M+1)⁺

Substantially the same procedure as in Example 5 was repeated using 34 mg of Compound (G) to give 18.7 mg of Compound II-51.

20 ¹H-NMR (CDCl₃) δ (ppm): 1.300(3H, t, J=7.4Hz), 1.325(3H, t, J=7.4Hz), 2.185(3H, s), 2.514(1H, dd, J=4.8, 14.5Hz), 2.540(2H, q, J=7.4Hz), 2.555(2H, q, J=7.4Hz), 3.384(1H, dd, J=7.5, 14.5Hz), 3.941(2H, s), 3.976(2H, s), 4.094(3H, s), 4.836(1H, d, J=16.4Hz), 4.910(1H, d, J=16.3Hz), 5.781 (1H, s), 6.845 (1H, dd, J=4.8, 7.5Hz), 7.371-7.843(5H, m), 8.998(1H, s)

25 FAB-MS (m/z): 616 (M+1)⁺

Substantially the same procedure as in Example 17 was repeated using 30 mg of Compound (H) to give 20.4 mg of Compound II-56.

30 ¹H-NMR (CDCl₃) δ (ppm): 1.280(3H, t, J=7.4Hz), 2.144(3H, s), 2.391(1H, dd, J=4.9, 14.5Hz), 2.517(2H, q, J=7.4Hz), 3.320(1H, dd, J=7.4, 14.5Hz), 3.885(2H, s), 4.069(3H, s), 4.521 (1H, d, J=16.3Hz), 4.631(1H, d, J=16.7Hz), 4.804(2H, s), 5.769(1H, s), 6.830 (1H, dd, J=4.8, 7.4Hz), 7.375-7.771(5H, m), 8.934(1H, s)

FAB-MS (m/z): 572 (M+1)⁺

35 Example 7

Compound IV-2

40 Compound (J) (Japanese Published Unexamined Patent Application No. 120388/87) (50 mg, 0.09 mmol) was dissolved in a mixture of 0.5 ml of trifluoroacetic acid and 50 μl of 3N HCl, and the solution was stirred at room temperature for 2 days. The precipitates were collected by filtration and subjected to high performance liquid chromatography (Unisil ₅C₁₈; methanol/water = 8/2) to give 8.4 mg of Compound (IV-2).

¹H-NMR (DMSO-d₆) δ (ppm): 4.947 (2H, s), 7.300-8.010 (6H, m), 8.249(1H, s), 9.266(1H, d, J=2.0 Hz)

45 FAB-MS (m/z): 390 (M+1)⁺

Example 8

50 Compound II-45 can be prepared by the reaction steps shown in Fig. 3. The starting Compound (J) is disclosed in Japanese Published Unexamined Patent Application No. 120388/87.

Compound II-45

55 Compound (J) (200 mg) was dissolved in 1 ml of dimethylformamide, and then 0.25 ml of an aqueous solution of 23.5 mg of sodium hydroxide was added thereto, followed by stirring at room temperature of 4 hours. After 1N hydrochloric acid was added to adjust the pH of the solution to 1-2, the precipitates were collected by filtration to give 178 mg (yield 91%) of Compound (K).

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¹H-NMR (DMSO-d₆) δ (ppm): 1.965(1H, dd, J=4.8, 14.0Hz), 2.184(3H, s), 3.364(1H, dd, J=7.5, 14.0Hz), 5.029(1H, d, J=18.1Hz), 5.071(1H, d, J=18.0Hz), 7.133(1H, dd, J=4.9, 7.5Hz), 7.595-8.189(5H, m), 8.733(1H, s), 9.398(1H, d, J=2.1Hz)

Compound (K) (168 mg), was dissolved in 3 ml of pyridine, and then 0.44 ml (4.7 mmol) of acetic anhydride was added thereto, followed by stirring at room temperature for 4 days. After evaporation of the solvent, 4 ml of 1N hydrochloric acid was added to the residue, and the precipitates were collected by filtration to give 182 mg (yield quantitative) of Compound (L).

¹H-NMR (DMSO-d₆) δ (ppm): 1.684(3H, s), 2.135(1H, dd, J=4.9, 14.4Hz), 2.252(3H, s), 3.865(1H, dd, J=7.6, 14.5Hz), 5.063(2H, s), 7.255(1H, dd, J=4.9, 7.5Hz), 7.612-8.582(5H, m), 8.760(1H, s), 9.389(1H, d, J=2.1Hz)

Compound (L) (172 mg) was suspended in thionyl chloride, followed by stirring at 90°C for 4.5 hours. After evaporation of the solvent, diethyl ether was added to the residue and the precipitates were collected by filtration to give 180 mg of Compound (M).

Compound (M) (67 mg, 0.1 mmol) was dissolved in 2 ml of ethylene dichloride, and then 180 μl of aniline in tetrahydrofuran was added thereto under ice cooling, followed by stirring at the same temperature for 1 hour. After evaporation of the solvent, the residue was dissolved in a mixture of 2 ml of tetrahydrofuran and 0.5 ml of methanol, and then 1 ml of 1N NaOH was added thereto, followed by stirring at room temperature for 3 hours. To the solution was added 1N hydrochloric acid (1.2 ml) for neutralization, followed by dilution with tetrahydrofuran. The mixture was washed with a saline solution and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (chloroform/methanol = 98/2) to give Compound II-45 (13 mg from 56 mg of isolated Compound N).

¹H-NMR (DMSO-d₆) δ (ppm): 2.110(1H, dd, J=4.9, 13.9Hz), 2.175(3H, s), 5.019(1H, d, J=18.1Hz), 5.088(1H, d, J=18.0Hz), 6.887(1H, s), 7.119-8.201(11H, m), 8.711(1H, s), 9.391(1H, d, J=2.2Hz), 10.071(1H, s)

FAB-MS (m/z): 687 (M+1)⁺

The following illustrates the effect of K-252a and functional derivatives thereof in the spinal cord ChAT assay, to determine their relative efficacy. Choline acetyltransferase (ChAT) activity was assayed in dissociated spinal cord cultures prepared from fetal rats by standard methods (see below). ChAT is the enzyme that catalyses the synthesis of the neurotransmitter acetylcholine, and is a specific biochemical marker for cholinergic neurons. In the spinal cord, the large majority of cholinergic neurons are motor neurons. Assay of this enzyme may thus be used as an indication of the effects of a factor (or factors) on the survival of cholinergic neurons and/or regulation of this enzyme.

Experiments with dissociated cultures of fetal rat spinal cord cells were performed generally as described (Smith *et al*, J. Cell Biol. 101:1608-1621, 1985). Dissociated cells were prepared from spinal cords dissected from day 14 embryonic rats by standard techniques known to those skilled in the art, using trypsin dissociation of tissue (Smith *et al*, 1985). Cells were seeded (plated) at 6 x 10⁵ cells/cm² in poly-1-ornithine coated plastic tissue culture wells in serum-free N2 medium and incubated at 37°C in a humidified atmosphere of 5% CO₂/95% air (Bottenstein and Sato, PNAS USA 76: 514-517, 1979) for 48 hours. ChAT activity was measured using modifications of the Fonnum procedure (J. Neurochem. 24: 407-409, 1975) according to Ishida and Deguchi (J. Neurosci. 3:1818-1823, 1983) and McManaman *et al*, Dev. Biol. 125:311-320 (1988). Activity was normalised to total protein measured by the bicinchoninic acid/Cu⁺⁺ reaction (BCA protein assay reagent, Pierce, Rockland, Illinois, USA).

Figure 1 shows that several compounds defined herein increased ChAT activity at 300 nM. Compound II-21, was also active at 30 nM (30% enhancement of ChAT activity over basal levels). This compound was more potent than K-252a or the remaining analogues since none of these actively enhanced ChAT activity at 30 nM.

The following Table shows various compounds on ChAT activity in rat spinal cord cultures.

Compound	Spinal Cord ChAT Activity	
	300nM	30nM
K-252a	100	-
II-44	146	80
II-34	133	66
II-47	126	-

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(continued)

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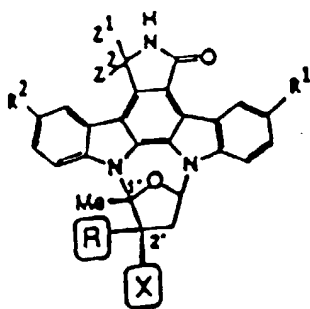
Compound	Spinal Cord ChAT Activity	
	300nM	30nM
II-1	122	-
II-31	120	-
II-29	118	65
II-32	118	70
II-38	118	-
II-2	111	NT
II-3	109	NT
II-46	109	84
II-5	104	NT
II-41	103	-
II-42	102	64
II-4	100	-
II-30	94	71
II-7	90	NT
II-39	90	-
II-36	86	-
II-8	85	-
II-9	83	64
II-10	81	143
IV-3	77	-
II-11	76	NT
II-21	76	63
III-1	75	-
II-12	75	-
IV-1	74	72
II-13	73	-
II-14	71	-
II-15	69	-
II-18	68	-
II-16	68	-
II-40	66	-
II-19	66	-
II-20	65	65
II-45	65	-
II-22	62	-
IV-2	62	NT
III-2	60	NT
II-25	58	-
II-23	55	-
II-24	50	-
II-26	39	-
II-33	-	77
II-43	-	125
II-49	-	62
II-51	130	53
II-56	88	53
II-48	70	-

(continued)

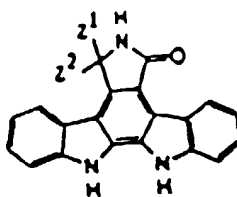
Compound	Spinal Cord ChAT Activity	
	300nM	30nM
NT = not tested at that concentration		
. = not active at that concentration		

Claims

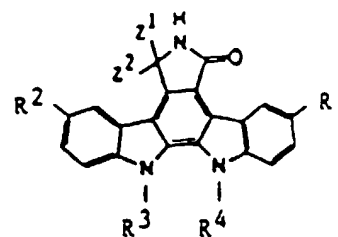
1. Use of a compound for the manufacture of a medicament for use in enhancing, in a mammal, the function of a cholinergic neuron, the compound being a functional derivative of K-252a, represented by the formula



(II)



(III)



or (IV)

wherein the following substitutions are made:

	Compound	R ¹	R ²	X	R	$\begin{matrix} Z^{1(1)} \\ Z^2 \end{matrix}$
5						
	II-1	H	H	CH ₂ N ₃	OH	H
	II-2	NHCONHC ₆ H ₅	H	CO ₂ CH ₃	OH	H
	II-3	CH ₂ SOC ₂ H ₅	H	CO ₂ CH ₃	OH	H
10	II-4	H	H	CH ₂ OH	OCH ₃	H
	II-5	H	H	CONHC ₂ H ₅	OH	H
	II-7(2,7)	H	H	CH ₂ NH-Gly	OH	H
	II-8	H	H	CON(CH ₃) ₂	OH	H
15	II-9(3)	H	H	-CH ₂ NHCO ₂ -		H
	II-10	Br	H	CO ₂ CH ₃	OH	H
	II-11	H	H	CONH ₂	OH	H
	II-12	H	H	CH ₂ OH	OH	H
	III-1	--	--	--	--	H
20	II-13	H	H	CONHC ₃ H ₇	OH	H
	II-14(2)	H	H	CH ₂ NH-Ser	OH	H
	II-15	H	H	CH ₂ SOCH ₃	OH	H
	II-16	H	H	CH=NOH	OH	H
	II-18(2,7)	H	H	CH ₂ NH-Pro	OH	H
25	II-19	H	H	CH=NNHC(=NH)NH ₂	OH	H
	II-20	Br	Br	CO ₂ CH ₃	OH	O
	II-21	H	H	CONH(CH ₂) ₂ OH	OH	H
	II-22	H	H	CO ₂ CH ₃	OH	O
	III-2	--	--	--	--	O
30	II-23	H	H	H	OH	H
	II-24	H	H	CH=NNHCONH ₂	OH	H
	II-25	H	H	CH ₂ OCOCH ₃	OH	H
	II-26(3)	H	H	-CH ₂ OC(CH ₃) ₂ O-		H
	II-29	NHCONHC ₂ H ₅	H	CO ₂ CH ₃	OH	H
35	II-30	CH ₂ SC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-31	Br	H	CH ₂ OH	OH	H
40						
45						
50						
55						

II-32	Br	Br	CO ₂ CH ₃	OH	H
II-33	CH ₂ SC ₆ H ₅	H	CO ₂ CH ₃	OH	H
II-34	Cl	Cl	CO ₂ CH ₃	OH	H
II-36	H	H	CONHC ₆ H ₅	OH	H
II-38	H	H	CH ₂ NHCO ₂ C ₆ H ₅	OH	H
II-39	NHCONHC ₂ H ₅	NHCONHC ₂ H ₅	CO ₂ CH ₃	OH	H
II-40	N(CH ₃) ₂	H	CO ₂ CH ₃	OH	H
II-41	CH ₃	H	CO ₂ CH ₃	OH	H
II-42	CH ₂ OCONHC ₂ H ₅	H	CO ₂ CH ₃	OH	H
II-43	NHCO ₂ CH ₃	H	CO ₂ CH ₃	OH	H
II-44	Br	Br	CH ₂ OH	OH	H
II-45	Br	Br	CONHC ₆ H ₅	OH	H
II-46	Br	Br	CONHCH ₂ CH ₂ OH	OH	H
II-47	CH ₂ OC ₂ H ₅	H	CO ₂ CH ₃	OH	H
II-48	CH ₂ N(CH ₃) ₂	H	CO ₂ CH ₃	OH	H
II-49	CH ₂ SO ₂ C ₂ H ₅	H	CO ₂ CH ₃	OH	H
II-51	CH ₂ SC ₂ H ₅	CH ₂ SC ₂ H ₅	CO ₂ CH ₃	OH	H
II-56	CH ₂ SC ₂ H ₅	CH ₂ OH	CO ₂ CH ₃	OH	H
IV-1 (4,8)	H	H	--	--	H
IV-2 (5)	Br	H	--	--	H
IV-3 (6)	H	H	--	--	H

(1) Z¹ and Z² are each hydrogen, or together represent oxygen, where indicated.

(2) NH-amino acid linkage is an amide bond through the carboxyl group of the amino acid.

(3) X and R are combined together to form the linking group.

(4) R³ is CH₂CH=CH₂; R⁴ is H.

(5) R³ and R⁴ are each H.

(6) R³ and R⁴ are each CH₂CH=CH₂.

(7) Compound is in the form of the hydrochloride.

(8) IV-1 is a 1.5 to 1.0 mixture of the

two components.

2. Use according to claim 1, wherein the medicament additionally comprises a neurotrophic factor.

3. Use according to claim 2, wherein the neurotrophic factor is a member of the neurotrophin family.

4. Use according to claim 3, wherein said member is nerve growth factor (NGF).

5. Use according to claim 1, for use in the treatment of Huntingdon's disease.

6. The compound of formula II-4 as defined in claim 1.

7. The compound of formula II-14 as defined in claim 1.

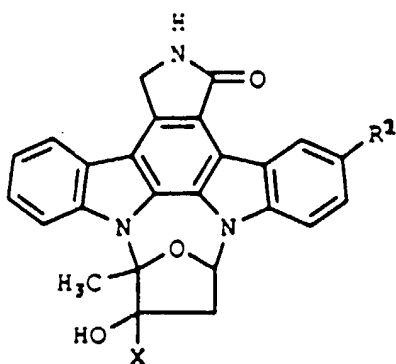
8. The compound of formula II-49 as defined in claim 1.

9. The compound of formula II-38 as defined in claim 1.

10. The compound of formula II-45 as defined in claim 1.

11. The compound of formula II-51 as defined in claim 1.

12. A compound of the formula (V):



(V)

wherein:

X represents CO_2R^5 or $\text{CH}_2\text{NHCO}_2\text{R}^6$;

R^1 represents hydrogen or $\text{CH}_2\text{SO}_2\text{R}^7$;

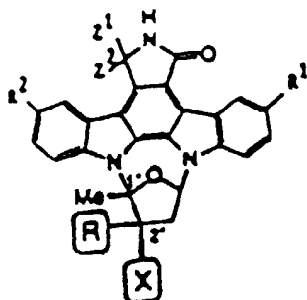
R^5 represents C_{1-6} alkyl;

R^6 represents C_{1-6} alkyl or C_{6-10} aryl; and

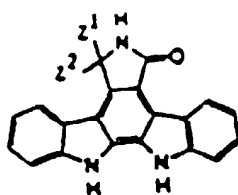
R^7 represents C_{1-6} alkyl; with the proviso that when $\text{X} = \text{CO}_2\text{R}^5$, R^1 is not hydrogen.

Patentansprüche

1. Verwendung einer Verbindung zur Herstellung eines Medikaments zur Anwendung in der Förderung der Funktion eines cholinergen Neurons in einem Säugetier, wobei die Verbindung ein funktionelles Derivat von K-252a ist, dargestellt durch die Formel

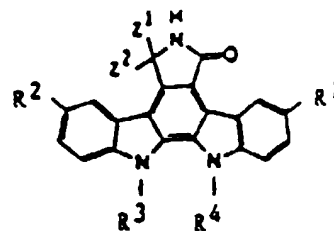


(II)



(III)

oder



(IV),

worin die nachstehenden Substitutionen vorgenommen sind:

Verbindung	R ¹	R ²	X	R	Z ¹ (1) Z ²
II-1	H	H	CH ₂ N ₃	OH	H
II-2	NHCONHC ₆ H ₅	H	CO ₂ CH ₃	OH	H
II-3	CH ₂ SOC ₂ H ₅	H	CO ₂ CH ₃	OH	H
II-4	H	H	CH ₂ OH	OCH ₃	H
II-5	H	H	CONHC ₂ H ₅	OH	H
II-7 (2, 7)	H	H	CH ₂ NH-Gly	OH	H
II-8	H	H	CON(CH ₃) ₂	OH	H
II-9 (3)	H	H	-CH ₂ NHCO ₂ -		H
II-10	Br	H	CO ₂ CH ₃	OH	H
II-11	H	H	CONH ₂	OH	H
II-12	H	H	CH ₂ OH	OH	H
III-1	--	--	--	--	H
II-13	H	H	CONHC ₃ H ₇	OH	H
II-14 (2)	H	H	CH ₂ NH-Ser	OH	H
II-15	H	H	CH ₂ SOCH ₃	OH	H
II-16	H	H	CH=NOH	OH	H

	II-18 (2, 7)	H	H	CH ₂ NH-Pro	OH	H
	II-19	H	H	CH=NNHC(=NH)NH ₂	OH	H
5	II-20	Br	Br	CO ₂ CH ₃	OH	O
	II-21	H	H	CONH(CH ₂) ₂ OH	OH	H
	II-22	H	H	CO ₂ CH ₃	OH	O
10	III-2	--	--	--	--	O
	II-23	H	H	H	OH	H
	II-24	H	H	CH=NNHCONH ₂	OH	H
	II-25	H	H	CH ₂ OCOCH ₃	OH	H
15	II-26 (3)	H	H	-CH ₂ OC(CH ₃) ₂ O-		H
	II-29	NHCONHC ₆ H ₅	H	CO ₂ CH ₃	OH	H
	II-30	CH ₂ SC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-31	Br	H	CH ₂ OH	OH	H
20	II-32	Br	Br	CO ₂ CH ₃	OH	H
	II-33	CH ₂ SC ₆ H ₅	H	CO ₂ CH ₃	OH	H
	II-34	Cl	Cl	CO ₂ CH ₃	OH	H
25	II-36	H	H	CONHC ₆ H ₅	OH	H
	II-38	H	H	CH ₂ NHCO ₂ C ₆ H ₅	OH	H
	II-39	NHCONHC ₂ H ₅	NHCONHC ₂ H ₅	CO ₂ CH ₃	OH	H
30	II-40	N(CH ₃) ₂	H	CO ₂ CH ₃	OH	H
	II-41	CH ₃	H	CO ₂ CH ₃	OH	H
	II-42	CH ₂ OCONHC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-43	NHCO ₂ CH ₃	H	CO ₂ CH ₃	OH	H
35	II-44	Br	Br	CH ₂ OH	OH	H
	II-45	Br	Br	CONHC ₆ H ₅	OH	H
	II-46	Br	Br	CONHCH ₂ CH ₂ OH	OH	H
40	II-47	CH ₂ OC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-48	CH ₂ N(CH ₃) ₂	H	CO ₂ CH ₃	OH	H
	II-49	CH ₂ SO ₂ C ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-51	CH ₂ SC ₂ H ₅	CH ₂ SC ₂ H ₅	CO ₂ CH ₃	OH	H
45	II-56	CH ₂ SC ₂ H ₅	CH ₂ OH	CO ₂ CH ₃	OH	H
	IV-1 (4, 8)	H	H	--	--	H
	IV-2 (5)	Br	H	--	--	H
50	IV-3 (6)	H	H	--	--	H

(1)Z¹ und Z² stehen jeweils für Wasserstoff oder bedeuten
zusammen genommen Sauerstoff, wo angegeben.

(2) Die NH-Aminosäurebindung ist eine Amidbindung über die Carboxylgruppe der Aminosäure.

(3) X und R sind gemeinsam zur Ausbildung der Verbindungsgruppe kombiniert.

(4) R^3 steht für $CH_2CH=CH_2$; R^4 bedeutet H

(5) R^3 und R^4 bedeuten jeweils H.

(6) R^3 und R^4 bedeuten jeweils $CH_2CH=CH_2$.

(7) Die Verbindung liegt in Form des Hydrochlorids vor.

(8) IV-1 ist ein 1,5: 1,0-Gemisch der beiden Komponenten.

2. Verwendung nach Anspruch 1, worin das Medikament zusätzlich einen neurotrophen Faktor umfaßt.

3. Verwendung nach Anspruch 2, worin der neurotrophe Faktor ein Glied aus der Neurotrophinfamilie ist.

4. Verwendung nach Anspruch 3, worin das Glied der Nervenwachstumsfaktor (NGF) ist.

5. Verwendung nach Anspruch 1 zur Anwendung in der Behandlung der Huntingdon-Krankheit.

6. Die Verbindung der Formel II-4, wie in Anspruch 1 definiert.

7. Die Verbindung der Formel II-14, wie in Anspruch 1 definiert.

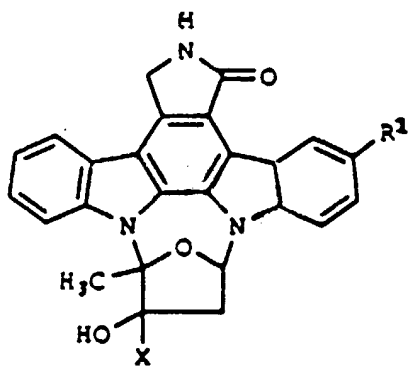
8. Die Verbindung der Formel II-49, wie in Anspruch 1 definiert.

9. Die Verbindung der Formel II-38, wie in Anspruch 1 definiert.

10. Die Verbindung der Formel II-45, wie in Anspruch 1 definiert.

11. Die Verbindung der Formel II-51, wie in Anspruch 1 definiert.

12. Eine Verbindung der Formel (V):



(V),

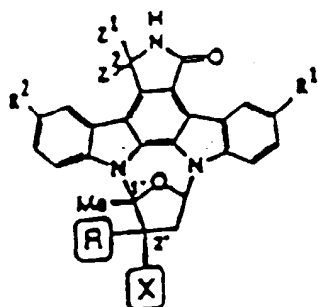
worin:

X für CO_2R^5 oder $CH_2NHCO_2R^6$ steht;
 R^1 Wasserstoff oder $CH_2SO_2R^7$ bedeutet;
 R^5 für C_{1-6} Alkyl steht;
 R^6 für C_{1-6} Alkyl oder C_{6-10} Aryl steht; und

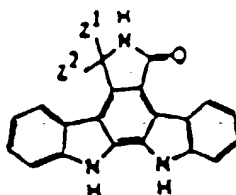
R^7 für C_{1-6} Alkyl steht; mit der Maßgabe, daß dann, wenn X für CO_2R^5 steht, R_1 nicht Wasserstoff ist.

Revendications

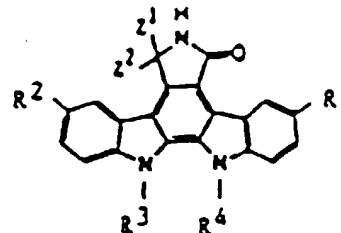
1. Utilisation d'un composé pour la fabrication d'un médicament à utiliser pour renforcer, chez un mammifère, la fonction d'un neurone cholinergique, le composé étant un dérivé fonctionnel de K-252a, représenté par la formule



(II)



(III)



ou (IV)

dans lequel on a effectué les substitutions suivantes:

	Compound	R ¹	R ²	X	R	Z ¹⁽¹⁾ Z ²
5						
	II-1	H	H	CH ₂ N ₃	OH	H
	II-2	NHCONHC ₆ H ₅	H	CO ₂ CH ₃	OH	H
10	II-3	CH ₂ SOC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-4	H	H	CH ₂ OH	OCH ₃	H
	II-5	H	H	CONHC ₂ H ₅	OH	H
	II-7(2,7)	H	H	CH ₂ NH-Gly	OH	H
	II-8	H	H	CON(CH ₃) ₂	OH	H
15	II-9(3)	H	H	-CH ₂ NHCO ₂ -		H
	II-10	Br	H	CO ₂ CH ₃	OH	H
	II-11	H	H	CONH ₂	OH	H
	II-12	H	H	CH ₂ OH	OH	H
20	III-1	--	--	--	--	H
	II-13	H	H	CONHC ₃ H ₇	OH	H
	II-14(2)	H	H	CH ₂ NH-Ser	OH	H
	II-15	H	H	CH ₂ SOCH ₃	OH	H
	II-16	H	H	CH=NOH	OH	H
25	II-18(2,7)	H	H	CH ₂ NH-Pro	OH	H
	II-19	H	H	CH=NNHC(=NH)NH ₂	OH	H
	II-20	Br	Br	CO ₂ CH ₃	OH	O
	II-21	H	H	CONH(CH ₂) ₂ OH	OH	H
	II-22	H	H	CO ₂ CH ₃	OH	O
30	III-2	--	--	--	--	O
	II-23	H	H	H	OH	H
	II-24	H	H	CH=NNHCONH ₂	OH	H
	II-25	H	H	CH ₂ OCOCH ₃	OH	H
	II-26(3)	H	H	-CH ₂ OC(CH ₃) ₂ O-		H
35	II-29	NHCONHC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-30	CH ₂ SC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-31	Br	H	CH ₂ OH	OH	H
40						
45						
50						
55						

5	II-32	Br	Br	CO ₂ CH ₃	OH	H
	II-33	CH ₂ SC ₆ H ₅	H	CO ₂ CH ₃	OH	H
	II-34	Cl	Cl	CO ₂ CH ₃	OH	H
	II-36	H	H	CONHC ₆ H ₅	OH	H
	II-38	H	H	CH ₂ NHCO ₂ C ₆ H ₅	OH	H
10	II-39	NHCONHC ₂ H ₅	NHCONHC ₂ H ₅	CO ₂ CH ₃	OH	H
	II-40	N(CH ₃) ₂	H	CO ₂ CH ₃	OH	H
	II-41	CH ₃	H	CO ₂ CH ₃	OH	H
	II-42	CH ₂ OC ₂ NHC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-43	NHCO ₂ CH ₃	H	CO ₂ CH ₃	OH	H
15	II-44	Br	Br	CH ₂ OH	OH	H
	II-45	Br	Br	CONHC ₆ H ₅	OH	H
	II-46	Br	Br	CONHCH ₂ CH ₂ OH	OH	H
	II-47	CH ₂ OC ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-48	CH ₂ N(CH ₃) ₂	H	CO ₂ CH ₃	OH	H
20	II-49	CH ₂ SO ₂ C ₂ H ₅	H	CO ₂ CH ₃	OH	H
	II-51	CH ₂ SC ₂ H ₅	CH ₂ SC ₂ H ₅	CO ₂ CH ₃	OH	H
	II-56	CH ₂ SC ₂ H ₅	CH ₂ OH	CO ₂ CH ₃	OH	H
25	IV-1 (4,8)	H	H	--	--	H
	IV-2 (5)	Br	H	--	--	H
	IV-3 (6)	H	H	--	--	H

(1) Z¹ et Z² représentent chacun l'hydrogène, ou représentent ensemble l'oxygène lorsque cela est indiqué.

(2) La liaison NH-acide aminé est une liaison amide par l'intermédiaire du groupe carboxyle de l'acide aminé.

(3) X et R sont combinés ensemble pour former le groupe de liaison.

(4) R³ représente CH₂CH=CH₂; R⁴ représente H.

(5) R³ et R⁴ représentent chacun H.

(6) R³ et R⁴ représentent chacun CH₂CH=CH₂.

(7) Le composé se présente sous la forme de l'hydrochlorure.

(8) IV-1 est un mélange 1,5/1,0 des deux composants.

2. Utilisation selon la revendication 1, dans laquelle le médicament comprend de plus un facteur neurotrophe.

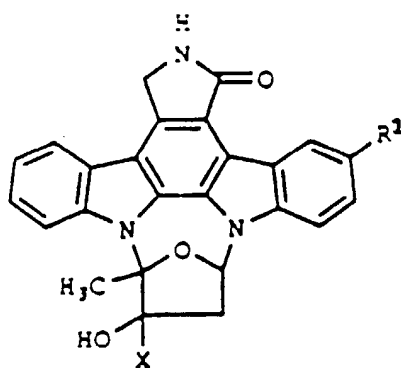
3. Utilisation selon la revendication 2, dans laquelle le facteur neurotrophe est un membre de la famille des neurotrophines.

4. Utilisation selon la revendication 3, dans laquelle ledit élément est le facteur de croissance des nerfs (NGF).

5. Utilisation selon la revendication 1, pour utilisation dans le traitement de la maladie de Huntington.

6. Composé de formule II-4, tel que défini dans la revendication 1.

7. Composé de formule II-14, tel que défini dans la revendication 1.
8. Composé de formule II-49, tel que défini dans la revendication 1.
- 5 9. Composé de formule II-38, tel que défini dans la revendication 1.
10. Composé de formule II-45, tel que défini dans la revendication 1.
11. Composé de formule II-51, tel que défini dans la revendication 1.
- 10 12. Composé de formule (V):



(V)

dans laquelle:

X représente CO_2R^5 ou $\text{CH}_2\text{NHCO}_2\text{R}^6$;

R^1 représente l'hydrogène ou $\text{CH}_2\text{SO}_2\text{R}^7$;

R^5 représente un alkyle en C_1 à C_6 ;

R^6 représente un alkyle en C_1 à C_6 ou un aryle en C_6 à C_{10} ; et

R^7 représente un alkyle en C_1 à C_6 ; avec la condition que lorsque $\text{X} = \text{CO}_2\text{R}^5$, R^1 ne représente pas l'hydrogène.

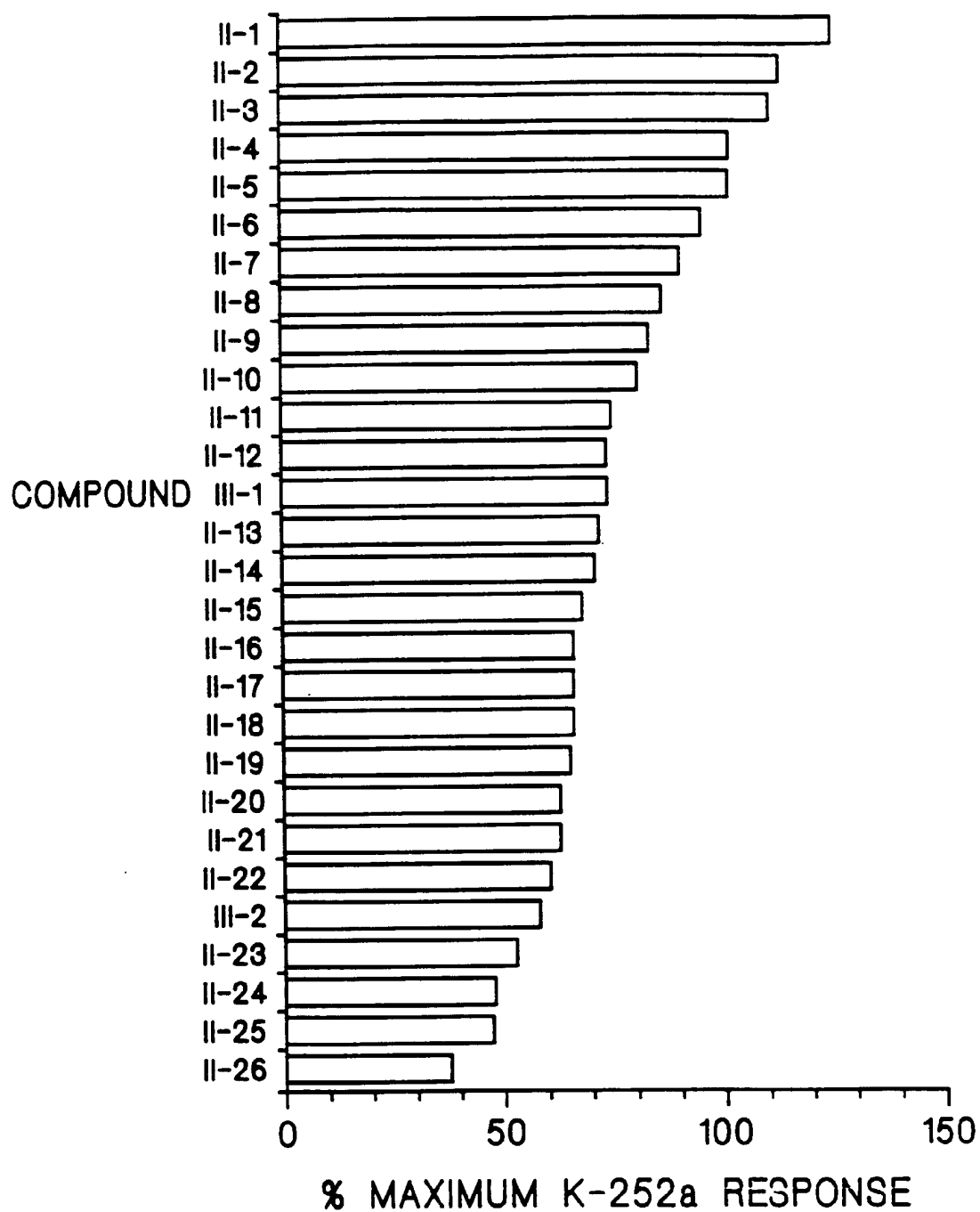


FIG. 1

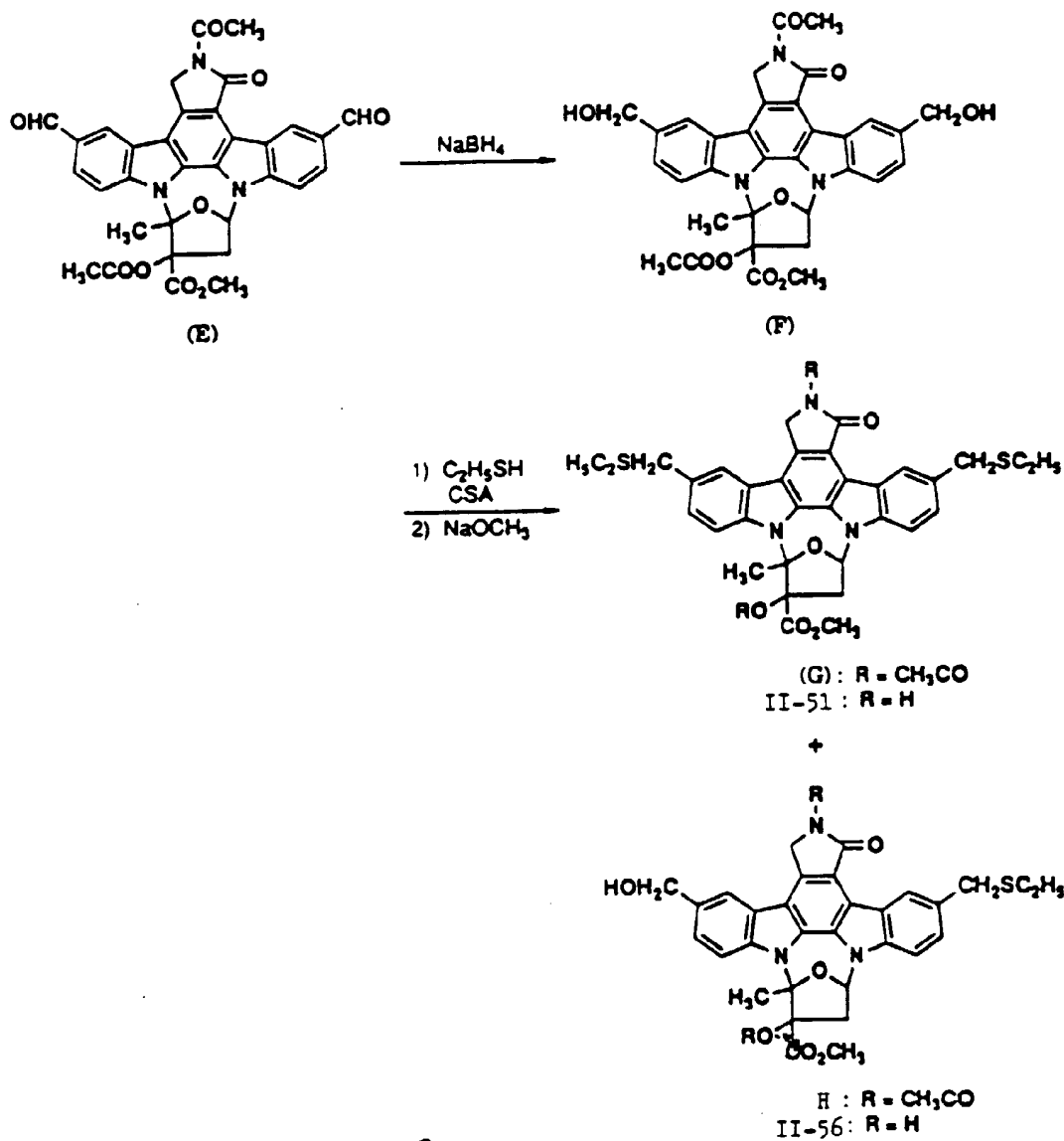
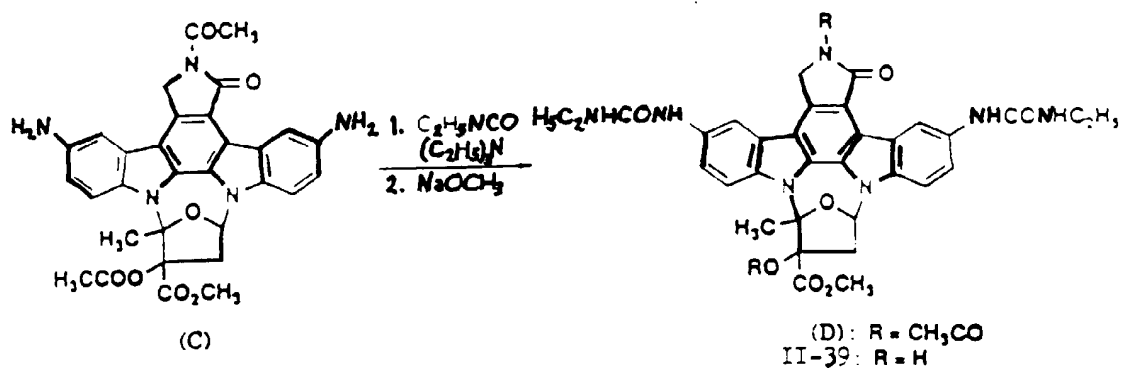


Fig. 2

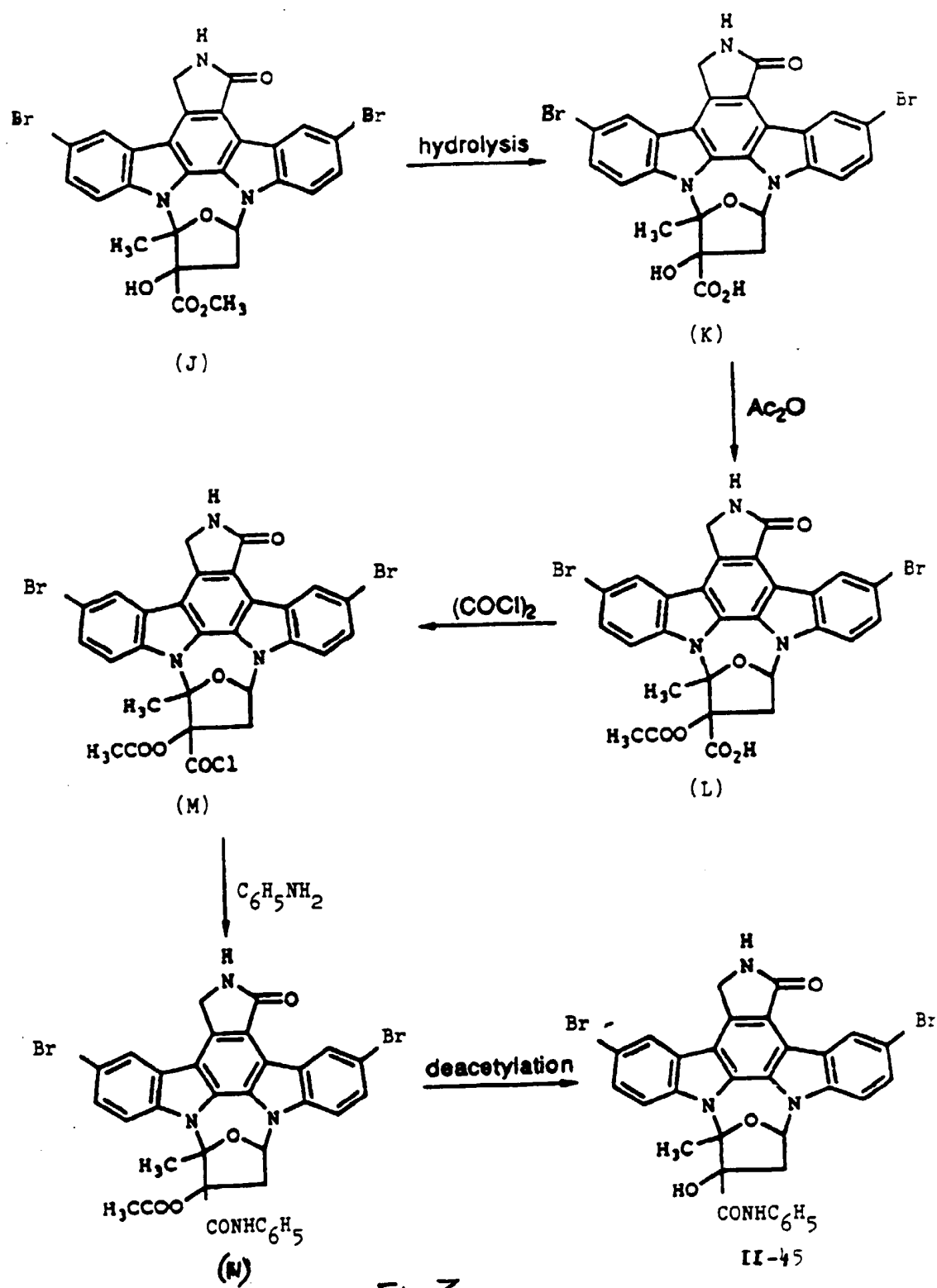


Fig. 3